EXPERT OPINION

Novel formulation and drug delivery strategies for the treatment of pediatric poverty-related diseases

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Introduction: Due to a lack of approved drugs and formulations, children represent the most vulnerable patients. Magistral, unlicensed formulations obtained by the manipulation of solid forms should undergo clinical evaluation to ensure bioequivalence. The development of new pediatric medicines is complex and faces technological, economic and ethical challenges. This phenomenon has contributed to the emergence of an adult–children gap. To improve the situation, the World Health Organization launched the global campaign 'Make medicines child size' and a number of international initiatives have been established. The situation is more critical in the case of poverty-related diseases (PRDs) that mainly affect poor countries.

Areas covered: This review critically discusses different strategies to develop pediatric formulations and drug delivery systems (DDS) in PRDs and their potential implementation in the current market. Readers will gain an updated perspective on the development of pediatric medicines for the treatment of PRDs and the proximate challenges and opportunities faced to ensure an effective pharmacotherapy.

Expert opinion: There is an urgent need for the development of innovative, scalable and cost-viable formulations to ensure pediatric patients have access to appropriate medications for PRDs. The guidelines of the International Conference on Harmonisation constitute a very good orientation tool, as they emphasize physiological and developmental aspects that need to be considered in pediatric research. It is important to consider cultural, economic and ethical aspects that make developing nations facing PRDs different from the developed world. Thus, the best strategy would probably be to conceive and engage similar initiatives in the developing world, to address unattended therapeutic niches.

Keywords: pediatric drug delivery and formulations, pharmacotherapy of poverty-related diseases

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1. Introduction

Before approval, medicines undergo extensive clinical evaluation to ensure safety, quality and efficacy. The World Health Organization (WHO) estimates that ~ 50% of the medicines prescribed for children are not commercially available in pediatric form [1].

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Article highlights.

- Due to a lack of approved drugs and appropriate formulations, children represent the most vulnerable of all the patient subpopulations.
- The pediatric market is smaller, riskier and less profitable than the one for adults, the development of novel pediatric medicines becoming increasingly unattended over the years. This phenomenon is more notorious in poverty related diseases (PRDs).
- International initiatives established to improve the situation of pediatric patients emphasize the need of a multidisciplinary and multisectoral research with focus on safety of pharmaceutical excipients, taste and flavor and formulation appropriateness.
- The oral route remains the easiest, most convenient and preferred drug administration route. Difficult dose adjustment and swallowing demands the development of novel liquid and small-size solid formulations where the taste is conveniently masked. Chewable, dispersible and orodispersible tablets (ODTs) represent approaches with great clinical potential.
- Innovative technologies such as oral strip technologies (OSTs) can be exploited for the transmucosal administration of drugs, though information regarding the relative permeability of the mucosa in children with respect to adults is scarce.
- Over the years, practitioners explored more reliable and non-painful methods (e.g., rectal, inhalatory and transdermal) for drug administration in children. Each route displays advantages and drawbacks and a more intense research is required to assess their real potential. Their implementation in PRDs is less feasible.
- The development of novel technology platforms based on micro- and nanotechnology may impulse this area. However, strategies should be scalable at the industrial setting and cost-viable to ensure patient affordability in PRDs.

This box summarizes key points contained in the article.

Due to a lack of approved drugs and appropriate formulations, children represent the most vulnerable patients [2]. Only one-fourth to one-third of the approved drugs have been labeled for treatment of all children [3,4].

Dose adjustment to body weight/surface and swallowing of solid forms are difficult in children younger than 5 – 7 years. When a commercial formulation is not available, adult solid forms are processed to produce magistral (unlicensed) formulations [2,5]. This practice can alter the stability of the drug in the gastrointestinal tract [6] or its pharmacokinetics (PK) [7]. Moreover, organoleptic properties such as bad taste that may reduce patient compliance are often neglected.

Forty million children in Europe are exposed to these medications annually [8]; a summary of unlicensed liquid formulations of cardiovascular drugs in the UK is reported elsewhere [9]. These medicines are not always prepared under harmonized protocols, raising serious concerns, especially in countries with constrained settings and deficient infrastructure and often more permissive regulations [10,11]. Moreover, unlicensed medicines should undergo clinical evaluation to ensure bioequivalence [12], a practice quite uncommon owing to the expense of clinical trials.

The development of new pediatric drugs/medicines became increasingly unattended over the years because the market is smaller, riskier and less profitable than the one for adults [13]. Zisowsky *et al.* have recently overviewed the regulatory requirements for the development of pediatric drugs from an industrial perspective [14].

Based on biological and metabolic changes taking place during development [15], the International Conference on Harmonisation (ICH) classifies the pediatric population in different subpopulations (**Table 1**) [16].

Preterm newborn infants constitute the most vulnerable and heterogeneous pediatric group owing to the substantial developmental changes during the last gestational weeks. This phenomenon makes clinical trials technically and ethically difficult. Term newborn infants do not show completely developed metabolic machinery, though the variability is less marked and clinical trials are more feasible. Based on different cognitive abilities and the capacity to use different dosage and pharmaceutical forms, schoolchildren can be also subdivided into two subgroups: i) pre-school children (2 – 5 years) and ii) schoolchildren (6 – 11 years). Furthermore, each subgroup displays differences in the gastrointestinal pH, transit, intestinal motility and conjugation and transport of bile salts with respect to adults [15], making the design of drug delivery systems (DDS) complex and the target population very restricted [17]. The most appropriate formulations according to age are summarized in **Table 2** [18,19].

The lack of pediatric R&D is more dramatic in poverty-related disease (PRDs; e.g., HIV/AIDS, tuberculosis (TB) and malaria) due to lesser profitability [20-23]. In 2007, the WHO launched the global campaign 'Make medicines child size' that aims to promote the development of pediatric formulations of drugs used in the treatment of infections affecting mainly developing nations [24].

However, the legal and regulatory requirements to conduct clinical trials in children are stricter than in adults [2] and recruitment of pediatric volunteers is not free of ethical dilemmas due to the involvement of parents [25-27].

Different sources in the USA have identified the need for at least 70 – 100 formulations for oral administration in neonates and infants [2,28]. However, it is unclear whether these surveys emphasized the needs of PRDs that do not primarily affect the American population.

To promote pediatric research, in 1997 and 1998, the US Food and Drug Administration (FDA) introduced regulatory measures and economic incentives [29]. The Pediatric Rule established that all the new drugs and biological products under clinical trial must also be trialed in children. Waivers can be obtained for drugs that are not likely to be used in children. This point is controversial as waivers are drug based and not target based [30]; a drug developed for breast cancer could obtain a waiver despite the fact that it could be effective for another pediatric cancer.

Table 1. Classification of the pediatric population according to ICH guidelines [16].

Classification	Age range	Observations
Preterm newborn infants	-	This category is not a homogeneous group of patients. A 25-week gestation (500 g) newborn is very different from a 30-week gestation newborn (1500 g). A distinction should also be made for low-birth-weight babies as to whether they are immature or growth retarded. These patients present important points that should be considered: i) gestational age at birth and age after birth; ii) renal and hepatic immaturity; iii) protein binding; iv) penetration of drugs into the CNS; v) rapid and variable maturation of all physiologic and pharmacologic processes leading to different dosing regimens with chronic exposure.
Term newborn infants	0 – 27 days	Although term newborn infants are developmentally more mature than preterm newborn infants, many of the physiologic and pharmacologic principles discussed above also apply to term infants. Volumes of distribution of drugs may be different than in older pediatric patients because of different body water, fat content and high body surface area:weight ratio. The BBB is still not fully mature and some drugs and endogenous substances (e.g., bilirubin) may gain access to the CNS with possible toxicity. Hepatic and renal clearance mechanisms are immature and rapidly changing; doses may need to be adjusted over the first weeks of life.
Infants and toddlers	28 days – 23 months	In this stage rapid CNS maturation, immune system development and total body growth are observed. Oral absorption becomes more predictable. Hepatic and renal clearance pathways continue to mature rapidly. After the first year of life, clearance of many drugs on a mg/kg basis may exceed adult values. There is often considerable inter-individual variability in this period
Schoolchildren*	2 – 11 years	Hepatic and renal clearance are mature, with clearance often exceeding adult values. In this period, psychomotor development could be adversely affected by CNS-active drugs. Factors useful in measuring the effects of a drug on children include skeletal growth, weight gain, school attendance and school performance. The onset of puberty is highly variable and occurs earlier in girls, in whom normal onset of puberty may occur as early as 9 years of age. Puberty can affect the apparent activity of enzymes that metabolize drugs, and dose requirements for some drugs on a mg/kg basis may decrease dramatically (e.g., theophylline).
Adolescents	12 – 16/18 years	In this period, drugs may interfere with the actions of sex hormones and impede development. This is also a period of rapid growth and continued neurocognitive development. Medicinal products and illnesses that delay or accelerate the onset of puberty can have a profound effect on the pubertal growth spurt and may affect final height. In this stage, adolescents assuming responsibility for their own health and medication. This causes a non-compliance, particularly when medicinal products (e.g., steroids) affect appearance. Recreational use of unprescribed drugs, alcohol and tobacco should be specifically considered.

*The schoolchildren group can be further subdivided into two groups: i) pre-school children (2 – 5 years) and ii) schoolchildren (6 – 11 years).

BBB: Blood–brain barrier; CNS: Central nervous system; ICH: International Conference on Harmonisation.

The European Medicines Agency (EMA) has also articulated a more 'empathetic' regulation that encourages pharmaceutical companies to conduct pediatric research: i) a reward of a 6-month extension to the supplementary protection certificate for the whole use of the product in adults also and ii) 8 + 2 years of data exclusivity on the pediatric use of the product for new studies via a pediatric use marketing authorization [31]. The EMA emphasized the relevance of formulations in pediatrics by establishing the Pediatric Committee's (PDCO)-Formulation Working Group that supports the activities of the committee and reviews formulations proposed in pediatric investigation plans. However, this legislation was implemented one decade later than in the USA, leading to a widening of the adult–children gap [32]. Another controversial issue is the disagreement between the US and the EU regulations on the acceptance of pharmaceutical excipients and their concentrations in children [33]. For example, the FDA restricts the ethanol content to a few formulations and only when the drug needs to be solubilized; the maximum content in over-the-counter formulations is 0.5, 5 and 10% for children < 6 years of age, 6 – 12 years and < 12 years, respectively. The EMA is more permissive, so the use of ethanol is common and the maximum allowance is 3 g/dose (oral or parenteral), with concentrations > 100 mg/dose being regarded as unsafe [34].

A number of initiatives increased the research in pediatrics. The Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) founded the Pediatric Formulation Initiative (PFI) to address the lack of appropriate pediatric formulations (http://www.nichd.nih.gov/). It relies on three pillars: i) scientific, ii) economics and iii) taste and flavor [35]. The European Paediatric Formulation Initiative (EuPFI) is another forum established in 2007 (http://www.eupfi.org/) that discusses challenges in the field, stating priorities and preparing recommendations. The EuPFI initially addressed four aspects: i) pharmaceutical excipients, ii) taste masking and test assessment methods, iii) extemporaneous formulations and dispensing and iv) drug delivery devices [36]. A new work group on age appropriateness of formulations has been incorporated and a database on the pharmacology, toxicity and safety of excipients in pediatrics, EuPFI STEP database (http://www.eupfi.org/gpage11.html), is being built. This project aims to facilitate and coordinate efforts toward the development of appropriate pediatric formulations. Interestingly, both initiatives dedicate efforts to address the taste and palatability of drugs [37]. More recently, the Global Research in Paediatrics (GRIP) was founded (http://www.grip-network.org/) to develop a training program in pediatric clinical pharmacology and validate and harmonize research tools in pediatrics [38].

Different NGOs such as Médecines Sans Frontières (MSF), Treatment Action Group, The Clinton Foundation, The Bill & Melinda Gates Foundation and Drug for Neglected Disease initiative work to improve the perspectives of specific PRDs. However, progresses in PRDs are at relatively slow pace and the commercial availability of advanced formulations and DDS remains small.

The present article overviews and critically discusses the different strategies explored to develop novel pediatric medicines for administration by conventional and novel administration routes in the pediatric pharmacotherapy of the three most recurrent PRDs, namely HIV/AIDS, TB and malaria. Since non-parenteral administration routes represent the most compliant in children, parenteral formulations were out of our scope.

2. Oral administration

The oral route remains the preferred one, especially in chronic treatments [39]. It is painless and does not demand specialized personnel. However, most of the oral formulations are solid, making dose adjustment and swallowing a challenging process in small children. This aspect is crucial in the treatment of neonates and infants, where the most recommended formulations are liquid (**Table 2**) [18,19].

2.1 HIV/AIDS

HIV/AIDS represents the most deadly infection [40]. A smaller number of antiretrovirals (ARVs) approved for children with respect to adults [41] and a more limited commercial availability of liquids are crucial drawbacks. Also, many ARVs are approved for pediatric use by extrapolating data in adults [42]. In this context, the coordinated development of safe, proven and effective pediatric formulations and DDS remains a pending goal in HIV/AIDS [43,44]. Pediatric HIV has been almost eliminated in developed countries, leaving a very limited demand in markets where the greatest number of pharmaceutical companies is located [45]. Not surprisingly, most of the recent developments of medicines for pediatric HIV took place in India. On the other hand, manufacturers are not always quality-certified by the WHO. Adult fixed-dose combinations (FDCs) are produced by several certified manufacturers, while most of the pediatric FDCs have one certified manufacturer; FDCs are formulations that contain more than one drug.

Many initiatives have increased pediatric patients' access to HIV medication from 10% in 2005 to 38% in 2008. However, this is not only a matter of quantity but also of quality, as often children in the poorest countries can afford only old and less effective ARVs. The same is true for more novel formulations. In this context, the evaluation of the patient affordability issue needs to be carefully asssessed because the best treatment quality is ensured only when patients can afford the whole spectrum of ARVs available in the market. In other words, affordability solely to old and cheaper ARVs cannot be put on the same level with affordability to all the ARVs irrespectively of their price.

Due to their higher physicochemical stability, easier storage and transportation, the most innovative pediatric HIV formulations available in the market are solids that enable easier dosing and swallowing.

Table 2. The most preferred pharmaceutical forms according to age, as defined by ICH guidelines [18,19].

Administration route	Dosage and/or pharmaceutical form	Preterm newborn infants	Term newborn infants (0 – 27 days)	Infants and toddlers (1 – 23 months)	Pre-school (2 – 5 years)	School (6 – 11 years)	Adolescents (12 – 16/18 years)
Peroral	Solution/Drops	☺	☺☺	☺☺☺	☺☺☺	☺☺	☺☺
	Effervescent	☺	☺☺	☺☺☺	☺☺☺	☺☺	☺☺
	Emulsion/suspension	–	☺	☺☺	☺☺☺	☺☺	☺☺
	Powders/granules/pellets*	–	😐	😐	☺☺	☺☺	☺☺☺
	Small tablets (3-5 mm)	–	–	–	☺	☺☺	☺☺☺
	Medium-sized tablets (5-10 mm)	–	–	–	–	☺	☺☺☺
	Large tablets (10-15 mm)	–	–	–	–	–	☺☺☺
	Very large tablets (>15 mm)	–	–	–	–	–	–
	Hard capsules‡	–	–	–	–	☺	☺☺☺
	ODts	–	😐	☺	☺☺	☺☺☺	☺☺☺
	CTs	–	–	–	☺	☺☺☺	☺☺☺
Transmucosal	STs	–	–	–	😐	☺	☺☺
Nasal	Solution	☺	☺☺	☺☺	☺☺	☺☺	☺☺
	Semisolid	☺	☺	☺	☺☺	☺☺	☺☺
Rectal	Suppositories	☺	☺☺☺	☺☺☺	☺☺	☺	😐
	Rectal enema	☺	☺☺	☺☺	☺	☺	😐
	Rectal capsules	☺	☺	☺☺	☺☺	☺☺	☺
Topical/ transdermal	Ointment, cream, gel	☺	☺☺	☺☺	☺☺☺	☺☺☺	☺☺☺
	Liquid	☺	☺☺	☺☺	☺☺☺	☺☺	☺☺
	Transdermal patch	😐	😐	😐	☺☺	☺☺	☺☺☺
Parenteral	i.v. solution§	☺	☺☺	☺☺	☺☺	☺☺	☺
	i.m.	☺☺	☺	☺	☺☺	☺☺	☺
	s.c.	☺☺	☺☺	☺☺	☺☺	☺☺	☺
	Pump system§	☺☺	☺☺	☺☺	☺☺	☺☺	☺
Inhalatory	Nebuliser	☺	☺	☺☺	☺☺☺	☺☺	☺
	MDI¶	☺	☺	☺☺	☺☺☺	☺☺	☺☺
	DPI	–	–	☺	☺☺	☺☺☺	☺☺☺
Ocular/ear	Eye drops	😐	☺	☺☺	☺☺	☺☺☺	☺☺☺
	Semisolid dosage form	😐	☺	☺☺	☺☺	☺☺	☺☺

☺☺☺: Dosage form of choice.
☺☺: Preferred acceptability.
☺: Applicable, but not preferred.
😐: Applicable with problems.
-: Not applicable.
*Powders, granules and pellets may be given to children from birth as a solution or, in specific cases, as dispersion.
‡Hard capsules that can be opened need to fulfill requirements for powders, granules and pellets, while soft capsules for solutions. Hard capsules that cannot be opened can be usually used in children older than 6 years.
§Preterm and term neonates may only accept very small volumes of medication to avoid volume overload.
¶A spacer and face mask might be required in younger children.
CT: Chewable tablet; DPI: Dry powder inhaler; ICH: International Conference on Harmonisation; i.m.: Intramuscular; i.v.: Intravenous; MDI: Metered dose inhalers; ODT: Orodispersible tablet; s.c.: Subcutaneous; ST: Sublingual tablet.

Orodispersible tablets (ODTs) are systems administered without external aid that disintegrate in saliva within 60 s (when placed on the tongue) and leave an easy-to-swallow suspension [46]. Fast disintegration is achieved owing to high porosity, wettability and incorporation of superdisintegrants. On the other hand, they are manufactured with low compression force what makes them friable and difficult to handle and package [47]. ODTs do not always lead to faster drug dissolution and absorption, though they overcome swallowing limitations in children above the age of 1 month as they can also be dispersed in a small amount of drinking water [48]. However, as strongly recommended by EMA, the safety and efficacy of ODTs that are swallowed intact or dispersed in large volumes of water is unknown and clear indications should be given in the summary of product characteristics (SmPC) and the patient information leaflet (PIL) [18]. *A priori*, dose adjustment is less feasible than in liquids. A key feature is that since they come in intimate contact with the oral mucosa, they need to display acceptable taste.

ODTs entered the market in the 1980s and their demand has grown steadily over the years [48]. Their performance is intimately associated with the technology employed for their production; current manufacturing and packaging equipment can be adapted to produce ODTs. These advantages resulted in a rich intellectual property portfolio [47], especially for preanesthesia and sedation [49,50], analgesia [51] and epilepsy [52]. The introduction of ODTs into the market was complemented with programs that educated patients and practitioners about the appropriate administration procedure where instructions such as 'do not swallow' or 'do not chew' need to be given. The incorporation of superdisintegrants in different stages of the production process and the use of different porogens enables the adjustment of porosity and disintegration rates [47,48,53]. On the other hand, it should be noted that the implementation of complex production procedures is time and energy consuming and it could lead to a substantial price growth that could affect affordability in PDRs. Regardless of the great potential and the broad spectrum of candidates proposed for this technology [48,49], only a very few ODTs are commercially available [52-55], probably because ODTs are more feasible for highly potent drugs. Thus, it is unclear whether they could be implemented in the treatment of PRDs that demand i) the administration of high and frequent doses and ii) cost-viable production processes. Having expressed this, more potent second-generation ARVs currently in the pipeline (e.g., rilpivirine) could be eventually formulated in ODT for children.

The same concept is employed to produce dispersible tablets (DTs). The main difference with ODTs is that they need to be primarily dispersed in water to form a physically stable suspension. DTs could be regarded as liquids at the administration time, though we include them among the solid forms. This technology has been more explored for HIV and other PRDs because they combine the main advantages of solid and liquid formulations that are optimal for administration in children from 0 to 8 years (**Table 2**) [18].

To reduce the risk of resistance development due to monotherapy, a number of pediatric dual and triple FDCs have been developed, mainly by Indian companies [56]. Stavudine and lamivudine DT (Lamivir-S baby/junior, Cipla Ltd., India) is a double FDC for use in children weighing less than 30 kg in combination with a solid stavudine/nevirapine/nevirapine FDC during the 14-day lead-in dosing of nevirapine (http://www.cipladoc.com/therapeutic/pdf_cipla/lamivir_s_baby_junior.pdf). As emphasized by EMA, dose adjustment with DTs will demand the fractioning of a 'fully dissolved solution or a homogeneous dispersion', this manipulation being prone to dosing mistakes [19]. To overcome this limitation, Kayitare *et al.* developed zidovudine (300 mg)/lamivudine (160 mg) rectangular DTs that can be broken into eight subunits, each subunit containing the drug required for 5 kg weight [57]. Tablets could be manually divided into pieces with very reproducible weight and were bioequivalent to the commercially available FDC Duovir® tablets Cipla Ltd., India. Padmavathi *et al.* developed a stavudine/lamivudine/nevirapine DT by means of a direct compression method [58]. Disintegration times as low as 20 s were attained. This work did not assess oral bioavailability and effectiveness. On the other hand, previous clinical investigations would support the feasibility of this formulation in children [59]. Based on these data, DTs represent one of the most promising systems for pediatric HIV.

Chewable tablets (CTs) are systems that can be chewed prior to swallowing and they do not necessarily demand water, though they require dentition. Thus, they are suitable for children older than 2 years [60]. Also here, taste masking is crucial to attain high patient compliance [61]. The bioavailability often depends on the chewing pace and strength. Formulations for the treatment of allergy (cetirizine, Zyrtec® McNEIL-PPC, Inc., USA) and asthma (montelukast, Singulair® MSD, USA) in children above the age of 2 years, respectively, are commercially available. For younger children, the same companies could develop oral granules.

In the context of HIV, didanosine chewable buffered tablets containing 25 – 200 mg are being commercialized with the brand name of Videx® (Bristol-Myers, USA). The broad drug payload enables the appropriate dose adjustment. However, they represent the only CTs in the market for PRDs.

The development of new formulations may also require the development, validation and implementation of new testing methods [62]. CTs can be swallowed without chewing, thus the dissolution test is the same used for regular tablets. However, CTs might not disintegrate appropriately. Thus, modifications in the test conditions might be demanded. Even though CTs show an interesting potential, they are not included in the guideline on pharmaceutical development of medicines for pediatric use [19].

The oral route remains the most popular and compliant administration. At the same time, swallowing is challenging in pediatric patients. In this context, new technologies (e.g., oral strip technology (OST)) have emerged. Oral strips are ultra-thin films made of hydrophilic polymers that rapidly dissolve on the tongue or the mouth. The administration

site is accessible, the delivery can be localized or systemic and the release fast. Also, several drugs can be incorporated in the same film. In addition, mucoadhesive oral strips can display more prolonged residence time and sustained release [63]. These advantages are relevant in pediatric patients that cannot swallow large tablets/capsules/pills. Oral strips also demand taste masking. A drawback is that the drug is absorbed by both transmucosal and intestinal absorption, this dual mechanism leading to great inter- and intra-subject variability and a more difficult prediction of the oral bioavailability, especially in children. Another disadvantage is its feasibility mainly for highly potent drugs, which is not the common situation in the first-generation ARVs. Technology Catalysts International (USA) forecasted that the OST market would grow remarkably [64]. On the other hand, only a few products have been commercialized. The future indicates that this delivery platform entails a promising business potential for pharmaceuticals and nutraceuticals, though its feasibility in pediatric PRDs is still doubtful. A strong indication is that OSTs are not included by EMA in the last draft guidelines [19].

Oral liquid preparations (OLPs) are formulations that are dispensed and administered as stable solutions or dispersions. They are considered as acceptable for children from birth and the most appropriate up to 8 years of age [16]. They need to be packaged with an appropriate administration/dosing device [19]. Their main advantage is that the dose can be fine-tuned. Conversely, there exists a risk of incorrect dosing. Interestingly, EMA emphasizes the danger of overdosing over underdosing. However, in HIV, the administration of subtherapeutic doses could lead to viral rebound and the appearance of resistance. The maximum single dosing volumes recommended for children below 4 years and between 4 and 12 years are 5 and 10 ml, respectively, and the minimum dosing volume will be determined by the accuracy of the dosing device [19].

Micro/nanotechnology has emerged as useful tools to improve the solubility, stability and bioavailability of drugs. Developments at the interface of micro/nanotechnology and pediatric drug delivery are restricted to a few reports in the scientific literature, probably owing to the complexities and the more limited economic appeal of the pediatric market.

Nanosuspensions are colloidal dispersions of pure drug nanoparticles stabilized with surfactants [65] obtained by different top-down and bottom-up techniques [65,66]. They represent the simplest nanotechnology to improve solubility of poorly water-soluble drugs. Some advantages are greater physicochemical stability and improved oral bioavailability than other liquid formulations. In addition, taste issues can also be overcome. A few pure drug nanoparticles of ARVs have been reported [67]. Van Gyseghem *et al.* improved the solubility of rilpivirine, a new ARV candidate in Phase III clinical trials, toward the development of a fast-dissolving pediatric powder for reconstitution [68]. *In vivo* assays in Beagle dogs showed faster absorption and significantly shorter lag time with respect to a tablet. The clearance mechanism was not altered. Even though the formulations were bioequivalent, the powder enables a better adjustment of the dose and an easier swallowing that the solid form.

Polymeric micelles are very versatile nanocarriers to improve the biopharmaceutic properties of drugs [69,70]. They display an inner hydrophobic core and an outer hydrophilic corona. The core enables the encapsulation of hydrophobic drugs, leading to improved water solubility and physicochemical stability. Polymeric micelles are feasible for oral administration [71]. Efavirenz (EFV) is a first-line ARV recommended by the WHO for children older than 3 years [72]. Due to the poor aqueous solubility and variable pharmacogenetics, relatively low oral bioavailability [73,74] and high inter- and intra-subject variability [75-77] are observed. Therapeutic drug monitoring (TDM) and dose adjustment represent crucial steps to ensure the efficacy and safety with EFV [78]. A commercial pediatric EFV solution (30 mg/ml) in a medium chain triglyceride (Miglyol 812) displays an oral bioavailability 20% smaller than that of a solid form [79]. The chronic administration of Miglyol 812 produces diarrhea and weight loss in rats, making this excipient probably inappropriate for children [80]. The elevated toxicological risk of children exposed to a broad variety of excipients approved for adults is a well-known phenomenon [81,82]. Even though EFV was approved by the FDA in 1998, the need for appropriate pediatric formulation has been recently stressed in the MSF list [83].

To improve the bioavailability and reduce the variability, Sosnik and collaborators recently developed a novel pediatric formulation by means of encapsulation within linear and branched poly (ethylene oxide)–poly(propylene oxide) PEO–PPO polymeric micelles [84-87]. Preclinical investigations showed a statistically significant increase of the oral bioavailability with respect to a suspension and an oily solution (**Figure 1**) [86]. In addition, an appropriate combination of sweeteners and flavors improved the characteristic burning mouth syndrome (BMS) provoked by EFV [87]. A clinical protocol that will compare the oral bioavailability of this formulation in adult healthy volunteers with that of capsules is currently under evaluation by the Argentine regulatory agency (ANMAT). This formulation could result in i) easier dosing and swallowing, ii) greater bioavailability and iii) smaller variability, than the existing formulations and could become one of the first nanomedicines for the treatment of pediatric HIV [21]. The potential extrapolation of this technology to other drugs needs to be proven.

Liquids remain the most advantageous formulations to fine-tune the dose of drugs with narrow therapeutic window and demanding TDM, especially in children. On the other hand, due to a smaller physicochemical stability they may need refrigeration and they are usally packed in large bottles that are difficult to carry home and store. Also, measuring volumes may be challenging in constrained-setting countries. To overcome these constraints, liquids could be supplied as powders for extemporaneous reconstitution and packed in individual containers [19]; for example, EFV-loaded micelles could be freeze-dried and resuspended

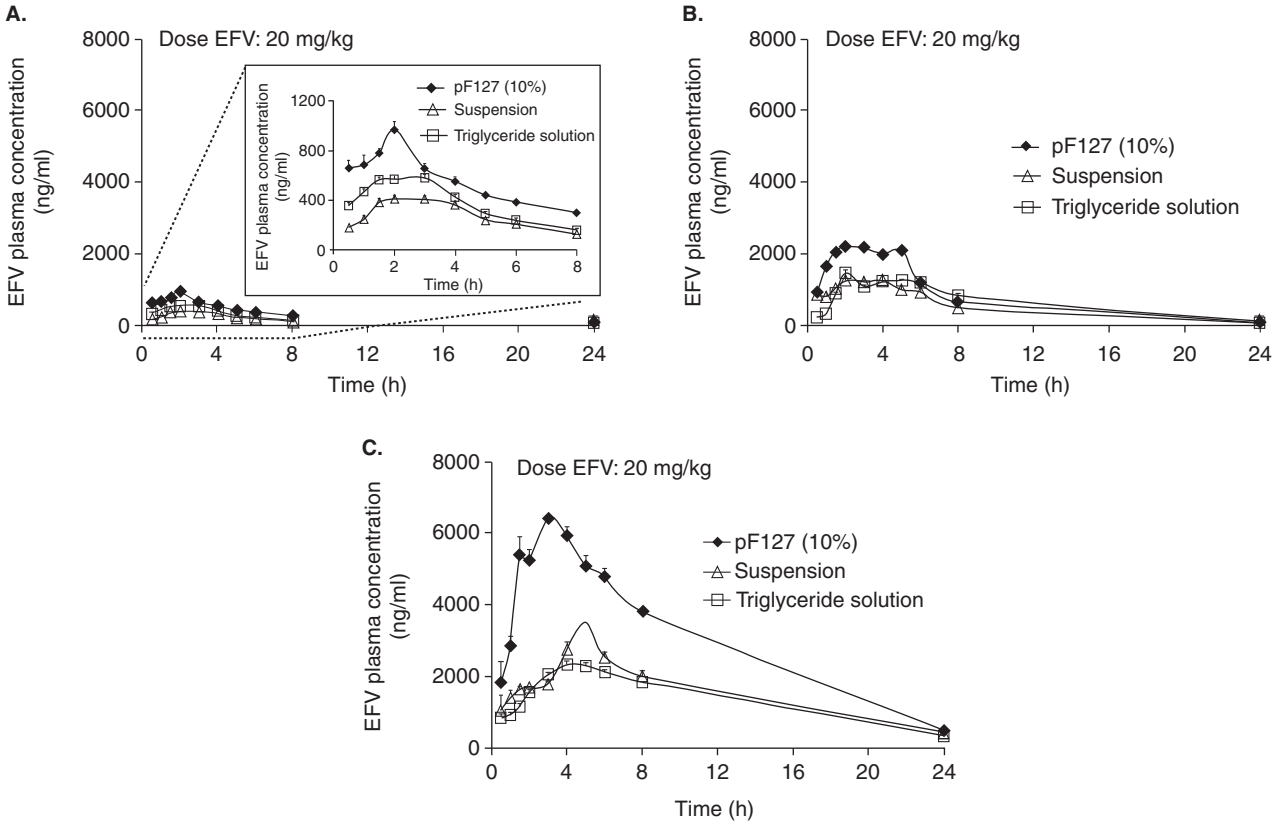

Figure 1. Efavirenz (EFV) plasma concentration after the oral administration of (A) 20 mg/kg, **(B)** 40 mg/kg and **(C)** 80 mg/kg. Results are expressed as mean ± S.E. (n = 8).
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without any detrimental effect [84,87]. On the other hand, as other dispersible forms, they demand access to potable water and the supply of a dosing device.

In an interesting approach, a modified liquid form of the antiviral famciclovir was developed to ease storage and improve stability [88,89]. The system comprises hard gelatin capsules loaded with granules dispersible in OraSweet® syrup. Single-dose and multiple-dose PK profiles in children aged 1 – 12 years (divided in three age cohorts) indicated that the formulation was safe, well tolerated and effective against confirmed or suspected herpes simplex virus and varicella zoster virus infections. The feasibility of this technology in PRDs should be conveniently assessed as it encompasses the advantages of both solid and liquid formulations.

Additional approaches initially explored to develop pediatric formulations include drug-loaded nanocapsules [90], self-nanoemulsifying drug delivery systems (SNEDDS) [91], multiple emulsions [92] and organized lipid complexes such as LYM-X-SORB that form chylomicron-like particles in the stomach and that are absorbed through the lymphatic system in the proximal intestine [93]. However, these approaches have not been explored for PRDs. Moreover, these approaches have not always discussed the feasibility of the excipient's qualitative/quantitative composition in children.

As previously mentioned, unbearable taste could be one of the main limitations. Protease inhibitors (PIs) are extremely bitter first-line ARVs that alter the sense of taste and reduce patient compliance [94]. The commercially available lopinavir/ritonavir solution for oral (Kaletra® Abbott Laboratories, USA) use is a Trojan horse in the treatment of pediatric HIV. To overcome bitterness, a number of strategies were proposed [95]. For example, tablets obtained by melt-extrusion technology and low strength compression with different drug payloads that could be conveniently combined to adjust the dose. However, these tablets cannot be crushed to ease swallowing as the oral bioavailability is lost [96], so they are of limited versatility to treat the heterogeneous pediatric population.

Microencapsulation [95] and complexation with ion exchange resins [97] are other efficient alternatives. Chiappetta *et al.* developed Eudragit E100 (a cationic copolymer of dimethylaminoethyl methacrylate, butyl methacrylate and methylmethacrylate) microparticles loaded with indinavir sulfate monoethanolate that withstand the action of saliva and disintegrate under gastric-like conditions [98]. The technique was modified to also enable the encapsulation of indinavir free base. Palatability tests in healthy adult volunteers indicated that the bitterness was masked efficiently. As the size of these microparticles was smaller than

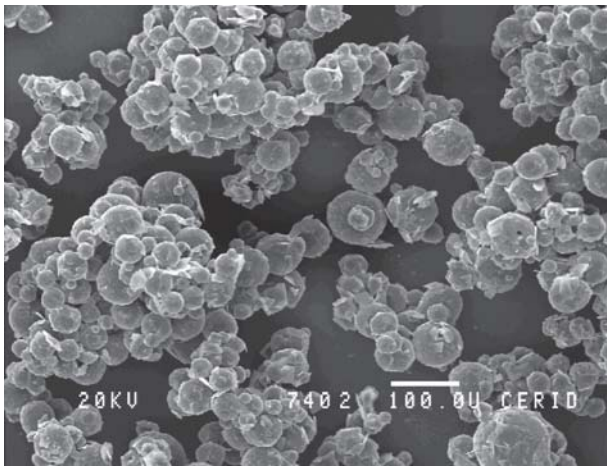

Figure 2. SEM microphotographs of Eudragit E100 microparticles loaded with 20% indinavir free base. Scale bar = 100 μm.

2 mm (**Figure 2**), they could be supplied in individual sachets (according to the dose) in the form of granules that can be dispersed in tap water and consumed orally [99]. Oral bioavailability studies are required to assess the clinical potential of this approach and its extension to other PIs. In addition, scale-up in an industrial setting, while keeping the price reasonable, should be conveniently evaluated. Otherwise, the chances of bench-to-bedside translation are low.

The oral mucosa and sensitivity of children and adults are different, thus taste tests in adults are of limited value [100]. In this context, new technologies (e.g., Astree electronic tongue, Alpha MOS, France) that aim to make bitterness evaluation more objective were introduced [100]. Even if very attractive, this technology is still unaffordable to academic research groups in developing countries.

Other liquid forms such as sprinkables, granules and pellets that are generated by the dispersion of solids in water could be important in pediatrics. However, reports in the literature are scarce. For example, didanosine is commercially available in granules and pellets produced with a parenteral coating that prevents degradation in the stomach.

In any event, these developments constitute a minor progress in the right direction because these experimental formulations need to undergo different types of screening by the WHO or FDA and clinical trials before receiving approval. Also, in some cases, PK data are available only in healthy adults or do not comply with the dose recommendations of the WHO [101].

Other PDRs are in a more disadvantageous situation due to a more limited drug discovery and formulation development.

2.2 Tuberculosis

With 2 billion infected patients, 9.2 million individuals who develop the disease every year and 1.7 million deaths, TB is the second most deadly infection [102,103]. The gold standard therapy comprises: i) Phase I (2 months) with rifampicin (RIF), isoniazid (INH), pyrazinamide and ethambutol and ii) Phase II (4 months) with RIF/INH [104,105]. Treatment interruption is a cause of therapeutic failure and development of multidrug-resistant TB (MDR-TB) [106]. Thus, despite that non-resistant TB is curable it remains the first cause of preventable deaths [107]. TB-infected children are also a high-risk population. In fact, RIF and INH are the only first-line drugs commercially available in pediatric formulation (**Table 3**). In the case of INH, the formulation is not commercially available worldwide. The development in this area is even scarcer and the extent of innovation is remarkably more limited. Different double and triple FDC DTs have been developed by Macleods Pharmaceuticals Ltd., India [108]; for example, INH/RIF (30 mg/60 mg and 60 mg/60 mg), INH/RIF/pyrazinamide (30 mg/60 mg/150 mg). Different superdisintegrants could be used to adjust the disintegration rate [109,110]. These approaches could also be implemented in children from birth because liquid suspensions can be prepared immediately before administration. However, oral bioavailability studies are still unavailable.

To reduce administration frequency and enhance patient compliance, various nanotechnologies have been explored in TB [20].

Pure drug nanosuspensions appear as those with the straightest potential translation into clinics [111]. On the other hand, since size reduction alters the PK, bioavailability studies need to be conducted first in adults and later on in children. Moretton *et al.* investigated the molecular features that govern the encapsulation of RIF within flower-like polymeric micelles for solubilization and physicochemical stabilization in contact with INH [112,113]. The degradation rate was reduced up to 4.4 times with respect to the free drug in gastric-like medium [114]. This platform could also be useful for the development of a RIF/INH FDC powder for re-dispersion.

Khuller and collaborators developed drug-loaded polymeric and lipid nanoparticles and administered them orally in murine TB models [115,116]. Remarkably, the administration of five oral doses of the drug-loaded nanoparticles every 10 days was effective to clear the mycobacterium like the daily administration of 46 doses of the free drugs [115,116]. A similar approach was followed by Swai *et al.* [117]. Even though these developments were not primarily conceived for children, any translation into clinics will necessarily benefit also the pediatric population, though in the longer range. Other oral forms such as ODTs and OSTs remain completely unexplored in TB.

2.3 Malaria

Malaria is the most prevalent parasitic disease in the world [118]; malaria accounts for 20% of the pediatric mortality in Africa [119].

Artemisinin combined therapies (ACTs) appear as the most effective strategy for the treatment of uncomplicated falciparum

Table 3. Commercially available pediatric formulations for TB.

Drug	Trade name (Company)	Dosage forms	Dose
Rifampicin	Rifaldin® (Sanofi-Aventis)	Suspension 20 mg/ml	Newborn (up to 1 month) 10 mg/kg/day, children 10 – 20 mg/kg/day, max dose 600 mg/day
Isoniazid	Isoniazid syrup (MIKART, Inc., USA)*	Syrup 50 mg/5 ml	10 – 15 mg/kg up to 300 mg/day in a single dose; or 20 – 40 mg/kg up to 900 mg/day, two or three times/week
	Isoniazid oral solution (Carolina Medical Products USA)‡	Solution 50 mg/5 ml	
Ciprofloxacin	Cipro® (Bayer)	Suspension 250, 500 mg/ml	20 – 30 mg/kg/day max dose: 1.5 g
Levofloxacin	Levaquin® (Ortho-McNeil-Janssen Pharmaceuticals, Inc.)	Solution 25 mg/ml	10 mg/day for older children, 15 – 20 mg/day for younger children
Linezolid	Zyvox® (Pfizer)	Suspension 20 mg/ml	10 mg/kg/dose every 8 – 12 h

*This formulation was discontinued.
‡Not commercially available worldwide.

malaria in young children [120]. ACTs are available as tablets and they pose problems related to swallowing, dosing and taste. Since young children are a high-risk group, the WHO stressed the urgent need to develop novel ACT pediatric formulations [121]. In this context, taste masked artemether–lumefantrine [122-124], artesunate–pyronaridine [125] and artesunate–mefloquine [126,127] suspensions, DTs and granules were clinically trialed in Phase III studies, representing the most remarkable and promising progress for oral therapy. Abdulla *et al.* developed pediatric arthemeter–lumefantrine DTs and compared their efficacy and safety with that of crushed commercially available tablets (Coartem® Novartis, Switzerland) in infants and children aged 0 – 12 years with uncomplicated malaria [123]. Both medications were bioequivalent. Interestingly, common adverse effects like vomiting were minimized with the DTs, though the reasons for this improvement were not established. In more recent studies, they evaluated the masking capacity of different flavors (cherry being the most effective) and extended the clinical trials [128,129]. Interestingly, the development of Coartem DT Novartis, Switzerland was carried out in partnership by Novartis and the Medicines for Malaria Venture. Strategies where academia/industry/NGOs join efforts to develop specific products will probably become the most efficient model in the future to increase the research pace in these less profitable niches.

As above-mentioned, several antimalarials are strongly bitter. Extrusion-spheronization is a versatile technology to produce taste-masked drug pellets for pediatric administration [130-132]. The technology is scalable and its cost-effectiveness should be evaluated case-by-case. Kayumba *et al.* used this method to produce pellets of quinine sulfate that were further coated with Eudragit EPO to mask its intense bitterness [133]; quinine is considered the bitterest drug. The drug was immediately released in the gastric-like medium. On the other hand, the gastric pH in neonates is close to neutral and becomes acidic only over the first year of life [17]. Thus, these differences should be identified and addressed.

Cyclodextrins (CDs) are cyclic oligosaccharides that display a hydrophobic cavity and a hydrophilic surface [134]. Drug/CD complexes are capitalized to improve water solubility, physicochemical stability and mask bad taste. CDs are more extensively used in Europe than in the USA, expressing divergences between FDA and EMA [135].

Shah and Mashru reported on artemether/β-CD complexes that were developed to make a liquid formulation palatable [136]. A sensory test revealed that the taste was completely masked. A similar approach was followed with primaquine phosphate that is active against exo-erythrocyte forms of *Plasmodium vivax* and *Plasmodium ovale* and the early pre-erythrocytic form of *Plasmodium falciparum* [137]. Complexes were used to formulate powders for re-suspension. It is noteworthy that the regulatory status of CD needs to be carefully evaluated as some of them may be not feasible in small children [138]; for example, CDs are considered safe for oral administration in children, though still a limited experience is available.

The development of oral forms from parenteral formulations is more challenging, though it could be useful to adjust a formulation for adults to one for children. α/β-Arteether (AE), an artemisinin derivative effective against MDR and severe falciparum malaria [139], is available as an intramuscular injection that can be painful and requires trained personnel, who are unavailable in rural areas, for administration. Tripathi *et al.* developed eight oral oily formulations of AE and tested the effectiveness in mice infected with MDR *Plasmodium yoelii nigeriensis* [140]. Cure extents ranged between 96 and 100% with no parasitemia rebound after 4 weeks.

A broad spectrum of nanotechnologies has been incipiently explored to develop advanced antimalarial formulations and vaccines [118]. The knowledge gained in these avenues will also benefit the pediatric population. Unfortunately, none of these developments has reached clinical stages.

3. Oromucosal (transmucosal) administration

The permeability of the oral mucosa is 4 – 4000 times more than that of the skin. Thus, a number of innovative technologies can be exploited for the oromucosal administration of drugs. On the other hand, information regarding the permeability of the oral mucosa in children is scarce. The EMA describes them very briefly in the oral administration section of the last draft [19]. To emphasize their pros and, more importantly, their cons, a separate section is dedicated to these systems here.

The successful implementation of nicotine chewing gums (CGs) in smokers led to their acceptance by the European Pharmacopeia [141]. The release is governed by the aqueous solubility of the drug, the chewing frequency and the hydration level of the gum. Main features are: i) CGs can be administered without water, ii) the release can be local (e.g., mouth, throat) or systemic and iii) the burst release can be minimized [142]. In addition, taste improvement can increase patient compliance in children [142]. As previously mentioned for systems that come into intimate contact with the oral mucosa, the taste needs to be conveniently masked [142]. CGs need to be chewed for at least 10 – 20 min, being more recommended for children older than 6 years. Although they have shown great potential, only a few pediatric CGs are available; for example, dimenhydrinate-loaded CG (10 mg, Travel-gum® Meda Pharma GmbH, Austria) is used for the treatment of motion sickness. Changes in salivary flow, chewing force and frequency make the release rate erratic. Moreover, even if the absorption is mainly transmucosal, it might also be intestinal, resulting in high inter-subject variability [143]. In this context, the usefulness of CGs seems limited to relatively potent drugs with a broad therapeutic window, which may not be the case of drugs used for the treatment of PRDs.

Sublingual tablets (STs) are formulations meant to be placed under the tongue, where they undergo fast disintegration and drug release, the drug being absorbed directly into the systemic circulation. It is possible to achieve high drug concentrations in plasma with a rapid onset of action. STs are solid and demand some level of training, thus they should be used only in children > 6 years or capable of maintaining the tablet in the right place without swallowing saliva for 1 min and eating for 5 min [18]. For instance, EMA anticipates lack of cooperation of children, coordination limitations and risk of choking and aspiration [18]. Also, since drug can be absorbed transmucosally or intestinally, the dosing is inaccurate. To date, pediatric STs are restricted to, for example, medicines to treat allergies in children above the age of 5 (Oralair® Stallergenes, France) [144] where dosing accuracy is less crucial than in infectious diseases. Based on the rarer experience gained in the implementation of other oromucosal delivery systems (e.g., mucoadhesive preparations, lozenges, etc.), formulations for oromucosal administration do not seem to represent, at least today, a real alternative in the therapy of PRDs.

4. Non-oral administration routes

Oral administration remains the most popular and preferred route. However, over the years, practitioners explored more reliable and less painful methods of drug administration. Reports describing the employment of 'off-label' routes of administration have proliferated [145]. Unfortunately, due to the frequent exclusion of children from company-sponsored clinical trials, these systems often remain 'off-label' and their potential adverse effects unidentified and uncharacterized. Harmonizing the development and production of these medicines remains an urgent challenge. Due to the greater profuseness of the research in oral formulations, a separate subsection has been dedicated to each PRD (Section 2). Conversely, the lack of R&D employing non-oral routes does not justify a separate section for each one.

4.1 Nasal administration

In general, nasal administration is intended to achieve localized effects. However, the nasal route is also an effective strategy to directly access the systemic circulation [18,146] and the central nervous system (CNS) [147,148]. A main constraint that probably hindered its clinical implementation for systemic/central delivery is the small volume that can be administered per nostril [149]. Thus, only very concentrated formulations or highly potent drugs are feasible. Depending on the age and the anatomy, different nasal forms may be preferred [18]; for example, drops for infants.

Only a few academic works explored it for the treatment of PRDs. Mainardes *et al.* encapsulated the first approved ARV, zidovudine, within poly(L-lactide) (PLA) and poly(L-lactide)/poly(ethylene glycol) (PLA/PEG) blend nanoparticles [150]. PLA/PEG systems increased the mean half-life in plasma by 7 h and the bioavailability by 1.3-fold with respect to the free drug. Touitou and coworkers evaluated the effectiveness of intranasal dihydroartemisinin in mice infected with

Plasmodium berghei ANKA, a model for severe malaria [151]. In this case, the drug was not encapsulated. Interestingly, survival rates in prophylaxis and treatment regimens were similar to those observed with the intraperitoneal administration.

CNS is one of the most challenging HIV reservoirs [152]. The virus may lead to HIV-1 encephalitis [153], a disease that is more frequent in neonates and children and where cognitive, motor and behavior effects impact notoriously the development capacities [154]. Thus, developing cost-viable strategies to target ARVs to the brain is gaining growing attention. Most of them use nanocarriers modified with a variety of ligands that are taken up selectively by cells of the blood–brain barrier (BBB) on intravenous injection. Employing the same platform developed to improve the oral bioavailability of EFV [84-87], Chiappetta *et al.* administered EFV-loaded micelles intranasally in rats and monitored brain concentrations by microdialysis [155]. The relative exposure index calculated by taking the ratio between the area under the curve in brain and plasma increased fivefold with respect to the same system administered intravenously. These are only incipient developments. The clinical assessment of this route for systemic and brain delivery, especially in children, seems at least questionable (if not unreasonable) and not deprived of ethical issues. On the other hand, it could be an effective and cheap way to surpass the BBB and increase the bioavailability in CNS.

4.2 Inhalatory administration

The inhalatory route is often used in children for the treatment of pulmonary diseases like asthma. For the systemic delivery of drugs (transpulmonary), inhalation is advantageous because it provides a large, thin and well-perfused absorptive surface area. In addition, it overcomes the hepatic first pass. Also, recent advances in aerosol technology that enable the fine control of dose delivery and deposition allowed the development of new inhaled DDS. Recommendations regarding appropriateness of devices according to age have been published [156-158], though in the case of children aged 0 – 5 years less evidence is available [18]. In some cases, the coordination or the ability to inhale strongly could condition the appropriate drug delivery. **Table 2** summarizes the appropriateness of each device to age according to EMA [18,19]. Most of the inhalers in the market were developed for adults and, only then used for the treatment of children with minor modifications. Moreover, many of the new devices are not approved for use in children. For instance, pressurized metered dose inhalers can be used in children from birth when combined with a spacer system and a face mask [18]. Older patients could use the inhaler with or without a spacer. In the case of dry powders, they could be acceptable in children > 1 year. Recently, EMA presented new guidelines on the requirements for clinical documentation for pediatric orally inhaled products [159].

To ensure the success of an inhalation device, it must fulfill the following requirements [160]: i) aerosol particles in the 0.5 – 5 μm mean aerodynamic diameter range to facilitate deposition in the deep lung; ii) reproducible aerosol particles; iii) solid drug particles (powders and suspension formulations) must dissolve in the lung lining fluid or adhere to the epithelium; iv) the released/solubilized drug must then partition and permeate the epithelial barrier to be released into the systemic circulation.

Due to the fact that TB is primarily (though not exclusively) a lung disease, this approach was proposed for the localized delivery of drug-loaded micro- and nanoparticles in pulmonary TB [20,161-163].

Khuller and collaborators evaluated the effectiveness of the same systems employed orally, and also administered by inhalation as dry powders [161-163]. They also targeted the main TB intracellular reservoir, the alveolar macrophages [164]. The robustness of these studies relies on their preclinical evaluation in TB models. Following the same approach, other groups produced polymeric microparticles that complied with the aerodynamic diameter range by means of different technologies [165-168]. Combining micro- and nanotechnology, Ohashi *et al.* produced rifampicin-loaded PLGA (poly(lactic-co-glycolic acid)) nanoparticles (150 – 330 nm) that were re-encapsulated in mannitol microspheres (2 μm) in one single step employing a four-fluid nozzle spray drier [169]. Once the nanoparticle-in-microparticle system reaches the lung, mannitol dissolves releasing the drug-loaded nanoparticles that are retained in the lungs for at least 12 h and taken up more selectively by alveolar macrophages. The effectiveness of this strategy would be uncertain in extrapulmonary TB. However, administration through the lungs could serve as a route for efficient systemic sustained release of drugs. Having expressed this, main drawbacks that may preclude translation into clinics in PDRs are more expensive production processes and the requirement of expensive administration devices that are not practical in poor countries. Also, the attainment of sufficiently high doses and systemic concentrations through this route could be problematic. On the other hand, in specific cases where greater and faster therapeutic success can be achieved, a more expensive and effective alternative should be appropriately pondered [43]. In any event, the oral route still appears as more compliant, especially in children.

4.3 Rectal administration

Rectal administration is a preferred route to reach the systemic circulation or when the oral route is not available or possible. In some cases, it can replace intravenous administration and since it is painless, greater patient compliance can be expected. It has a slow onset and more prolonged duration than intravenous administration. Depending on the area of the rectum where the drug is released and absorbed, the hepatic first pass can be overcome or not. A drawback is that due to differences in the venous hemorrhoidal circulation, inter-subject variability can be relatively high. It is important to design the formulation in size and shape adequate to children [16,18].

This route was proposed for ARVs that undergo i) fast degradation in the stomach or ii) hepatic first pass [170]. However, only a few studies employing the first approved ARV, zidovudine, were reported. A similar situation is observed in TB. For

example, Taki *et al.* investigated the PK of RIF-loaded suppositories in adult healthy volunteers with positive results [171], though no further developments were reported. Thus, it is quite improbable that this approach will make any progress to the clinics in HIV and TB.

Vomiting and unconsciousness are common symptoms of malaria. In these cases, oral formulations are not feasible. On the other hand, parenteral administration demands trained personnel who are quite unavailable in isolated areas. Thus, the administration of rectal forms of artesunate has been investigated over the last decades [172] and it is strongly recommended by the WHO guidelines [173]. A remarkable advantage is that the administration can be performed by caregivers or health workers with no training [174]. Artesunate 50 and 200 mg suppositories are commercially available and they are considered effective and safe as parenteral treatments. For example, Barnes *et al.* conducted a randomized study in African children and adults suffering moderately severe malaria and compared the effectiveness of artesunate suppositories and parenteral quinine [175]. With suppositories, parasitemia levels were significantly lower in both children and adults after 12 h. The clinical response was similar to that of quinine. Moreover, the drug was well tolerated and no neurotoxicity was observed. On the other hand, a great intersubject variability was measured and after the first rectal dose, the treatment needed to be completed with additional effective antimalarials as one single artesunate dose did not provide total cure; reappearance of parasites was detected after 1 week. Also, optimal conditions for rectal administration are still unclear and could vary among communities [174]. Additional evidence was reported by Pengsaa *et al.* who evaluated two regimens of rectal artesunate to treat children with cerebral/complicated malaria [176]. The drug was rapidly absorbed and plasma concentrations were within the therapeutic window. Even though several groups explored this approach, only a few assessed its effectiveness in children. More recently, Gaudin *et al.* developed a two-compartment artesunate (50 mg/g) mucoadhesive rectal gel for pediatric use [177]. This formulation could probably be more compliant because it adjusts and adheres better to the rectal physiognomy though the accurate dosing should be ensured. Even if an interesting piece of information, this work lacked *in vivo* data to support the clinical potential of the formulation. Overall, the potential of this route remains partially exploited.

4.4 Transdermal administration

The transdermal delivery is an attractive non-invasive route to administer often small, potent and lipophilic compounds that show significant transport across the skin with sustained release profiles. Other good candidates are drugs that require frequent injections or those that elicit gastrointestinal irritation or erratic efficacy absorption on oral administration. The skin serves as a very effective barrier and tends to confer a slow sustained PK profile that is best suited to medicines that require chronic or prolonged therapy; transdermals are considered 'needle-free' infusions. Other important advantage is that these systems can be self-administered without a special training and they can provide release for long periods of time (up to 1 week). Since the skin features permeability change from birth to adulthood going through the different developmental stages, a careful design needs to be undertaken to develop systems for children [18,19]. This aspect is also applicable in clinical trials as extrapolation of adult data will be extremely difficult. In addition, the application would be preferred in sites of body that cannot be reached by the child and touched, rubbed or removed. EMA recommends the development of single dose systems, though cutting could be implemented to adjust the dose in cases where cutting lines are present and the homogeneity of the drug payload across the device is ensured [19]. Also, patches are preferred over gels, ointments and creams because the dosing is more accurate. Despite the advantages, only a few pediatric products are available in the market and those for adults are not feasible in children [18,19]. Daytrana® Noven Therapeutics LLC, USA patch is the first once-a-day patch containing methylphenidate for treatment of attention deficit hyperactivity disorder (ADHD) in children aged between 6 and 12 years [178]. The device is applied in the hip and can be removed to shorten the effect and minimize side effects, enabling customized/flexible wear times for both long and short school days and weekends. It should be used only once a day for up to 9 h.

Due to the appealing features toward a chronic administration, some works explored the transdermal delivery of ARVs, as comprehensively overviewed by Ojewole *et al.* [170]. A majority assessed the delivery of nucleoside reverse transcriptase inhibitors, namely zidovudine, didanosine and zalcitabine. These studies are of very limited value because these drugs have gone a long way in the clinics [21] and thus the virus has developed resistance. Studies with more novel drugs would be required. Also, since ARVs are often large molecules and permeation/absorption is poor, most of these studies employed different vehicles, nanocarriers and permeation enhancers [170]. In a more recent study, Dubey *et al.* assessed the permeation of indinavir-loaded ethanolic liposomes through cadaveric skin with positive results [179]. Due to the high doses required and the lack of preclinical data together with greater costs, it seems a bit unrealistic that a system of this kind could make all the way to clinics and replace the oral therapy in pediatric HIV. A similar phenomenon is observed in TB and malaria, where only a few works can be found in the literature.

Another PRD that has not been the focus of the present review is the parasiticidal leishmaniasis that shows a mucocutaneous form that is being addressed employing transdermal delivery [180].

The transdermal market is dominated by patches, though other technologies such as the micro-needles and jet injectors are being incorporated to the portfolio [181]. Liquid jet injectors employ a high-speed jet to puncture the skin and deliver drugs without the use of needles [182-184]. Dörr *et al.*

administrated Genotropin® Pfizer, USA, a formulation for the treatment of pediatric growth deficiency, employing Genotropin ZipTip, a needle-free device, and with Genotropin Pen, a fine-gauge needle device [185]. The needle-free system was bioequivalent and 20% of the patients preferred to continue using it after the study. Enfuvirtide is a fusion inhibitor employed in HIV-infected children aged 6 – 16 years. Owing to instability in the stomach it is administered subcutaneously twice-a-day. This practice provokes local irritation and pain. A gas-powered needle-free drug delivery device (Biojector® 2000, Bioject Medical Technologies, USA) was clinically evaluated to ease the administration, though it was ultimately abandoned in 2007 due to insufficient improvement [186]. Furthermore, the cost of the medication can increase dramatically on the implementation of this device, a phenomenon prohibitive in the case of PRDs.

5. Expert opinion

Personalized medicine is a medical model that aims to tailor the pharmacotherapy to the needs of individual patients. It has been explored mainly in oncology though it could also be applied to diseases of the CNS, diabetes and autoimmune diseases [187]. In chronic infectious diseases such as HIV, the incorporation of pharmacogenetics would also enable to tailor the therapy to individual PK profiles, though this practice is expensive and of difficult implementation in constrained-resource countries. Innovation in pediatrics is still far from optimal. R&D programs are often oriented to solve specific (bio)pharmaceutical drawbacks and are of limited versatility. The situation in pediatrics is aggravated by the fact that safety data of some common generally referred as safe (GRAS) excipients in high-risk pediatric subpopulations (e.g., neonates) are still partially or completely unknown. Consequently, the breach between personalized medicine and the state-of-the-art remains profound, as stressed during the second conference of EuPFI in 2010 [188] and more recently in the third EuPFI conference and the PFI Workshop.

The market of PRDs is even smaller and less profitable, making the spectrum of technology platforms transferable to clinics narrower. The replacement of the oral route by alternative non-oral ones that have not been sufficiently explored seems a great challenge despite that some successful examples have been already translated into clinics in niches such as malaria. Similarly, the development of pediatric DDS (to replace conventional formulations) in PDRs that would improve patient compliance appears less feasible because innovative technologies are more expensive and less affordable.

Having expressed this, more 'empathetic' legislation and the foundation of multidisciplinary research networks gathering industry, academia, hospitals, NGOs and regulatory agencies point out more coordinated and complementary efforts to close the adult–children gap [189,190]. These initiatives will necessarily engage a conscious discussion to identify the most urgent needs in pediatrics and the most suitable strategies to address them. Furthermore, they will lead to the maximized capitalization of infrastructure, economic and human resources. The impact of these initiatives on the quality of the therapy in PRDs is still uncertain. On the other hand, it is worth mentioning that small innovations such as microencapsulation for taste masking – that from a scientific perspective might seem less sophisticated – could represent a substantial improvement of the therapy and the patient lifestyle.

ICH guidelines constitute a very good orientation tool as they emphasize physiological and developmental aspects that need to be considered to face research in pediatrics [16]. However, it will be always important to consider that there exist cultural, economic and ethical aspects that make developing nations suffering PRDs different from the developed world. Thus, the best strategy would probably be to conceive and engage similar initiatives in the developing world to address these unattended therapeutic niches. This would be a move in the right direction to guarantee the appropriate access of high-quality, safe and more effective pediatric medicines.

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